REMARKS

Claims 37-38 have been canceled without prejudice. Claims 32, 41, and 42 have been amended for greater clarity. Claims 52-53 have been added. Support for the claim amendments and new claims can be found throughout the specification (*e.g.*, page 15, lines 13-19; page 16, lines 12-29; and Figure 4) and original claims (*e.g.*, claim 38). No new matter has been introduced. Applicants' amendments are not made in acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

Applicants note that the Examiner has withdrawn the previous rejections under 35 U.S.C. § 102(b) (citing Vidaver *et al.*) and under § 103(a) (citing Noonberg *et al.*) in view of Applicants' Response filed on July 17, 2006.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Rejections of Claim 32-35, 37-46, and 48-51 under 35 U.S.C. § 112, First Paragraph

Claims 32-35, 37-46, and 48-51 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection and contend that the rejection is moot in light of the amended claims.

The Examiner asserts that "Applicants' claims are directed to a broad genus recombinant vectors (*e.g.*, viral, plasmid, etc.) that can infect host cells of any type (*e.g.*, human, bacterial, yeast, etc.) via any mechanism (*e.g.*, replicate, integrate, etc.). In addition, although said vectors must contain one or more recognition sites for a restriction enzyme, no limitation is placed on the type of restriction enzyme that may be used (*e.g.*, class I, class II, class IIs, etc.) . . . Applicants' specification provides only one example of a pSP-luc+ plasmid [containing] U1 and Bae1 "double cleavage" restriction site, i.e., Bae1/U1 construct." See Office Action, page 3, lines 8-15.

It appears that the Examiner's rejections are mainly directed to the recitations of the "recognition site" and "restriction enzyme" in the claims (see Office Action, page 4, line 14 through page 6, line 15). To support this contention, the Examiner asserts that "Applicants' arguments are not commensurate in scope with the claims. The claims are not limited to the

use of 'double restriction' enzymes that cleave outside of their recognition sites like BaeI. For example, Applicants' claims encompass the use of TypeI/III endonucleases, which have unpredictable cleavage sites." Office Action, page 7, lines 12-15.

Applicants reiterate the arguments already made of record and contend that the specification fully supports the claimed invention. Nevertheless, solely to expedite prosecution of the application, without acquiescing to the Examiner's assertion, Applicants have amended independent claims 32 and 42 to specify that the restriction enzyme is a dual cleavage restriction enzyme.

The Examiner further asserts that "Applicants do not disclose anything other than BaeI. However, Type I, II, III and even 'relaxed' forms of the enzyme fall within the scope of their claims. As shown by George et al., Lanio et al., and Brown, the art with regard to these other enzymes is inherently unpredictable. A person of skill in the art cannot reliably predict where the Type I/III enzymes will cut . . . Furthermore, Applicants' specification provide no guidance to alter or 'relax' enzymes to make the type of cuts specified in the claims." See Office Action, page 8, lines 3-19.

Applicants respectfully disagree. Although restriction enzymes are traditionally classified into three types, it is known in the art that Type II enzymes are the only class used in the laboratory for DNA analysis and gene cloning since they cut DNA at defined positions close to or within their recognition sequences and produce discrete restriction fragments and distinct gel banding patterns (see a printout from New England BioLabs website; enclosed herewith as **Exhibit A**). One of skill in the art would know that the claimed invention is useful for the DNA cloning technology and the recited restriction enzyme is a Type II enzyme, rather than a Type I/III enzyme, in light of the teachings of the specification. Applicants have added new dependent claims 52-53 to specify that the restriction enzyme is a Type II restriction enzyme.

Independent claims 32 and 42 as amended each relate to a recombinant vector comprising an isolated nucleotide sequence encoding an snRNA, wherein said nucleotide sequence has been modified to contain a recognition site for a dual cleavage restriction enzyme, such that digestion with a single restriction enzyme excises from said vector a restriction fragment which includes said recognition site and forms insertion sites in said

vector. One of skill in the art would know that the inventive portion of the claimed recombinant vector lies in the unique merging of technological features known in the art. For example, digestion with a single dual cleavage restriction enzyme excises from said vector a restriction fragment which includes said recognition site and forms insertion sites in said vector. As the specification sufficiently describes these characteristics of the genus of the claimed recombinant vectors of the invention (see, *e.g.*, page 15, lines 13-29; page 16, lines 1-26; Example on pages 21-23; and Figure 4), a skilled artisan would recognize that Applicants were in possession of the claimed invention.

Applicants submit that where, as in this case, (1) the inventive portion of the subject matter is disclosed and (2) any additional variability within the genus arises due to additional elements that are not part of the inventor's contribution, and when the level of knowledge and skill in the art would allow one skilled in the art to recognize that the applicant was in possession of the genus, the written description cannot be deemed defective. See Written Description Guidelines Training Materials available at, http://www.uspto.gov/web/offices/pac/writtendesc.pdf (released March 1, 2000, Example 8, page 35).

Applicants further point out that at the time this application was filed, various splicesome snRNAs (*e.g.*, U1 – U12) were well known in the art. See, *e.g.*, Mattaj, I.W. *et al.*, 1993, FASEB J 7:47-53 (Reference **AW2** in the Form PTO-1449 submitted on November 5, 2001). Also, various vectors were constructed utilizing snRNAs to deliver antisense targeting sequences for reducing gene expression in various cell types. See, *e.g.*, Abounader, R., *et al.*, 1999, J of NCI 91:1548-1556; Liu, D, *et al.*, 1997, J of Virology 71:4079-4085; and Montgomery, R.A., *et al.*, Hum Mol Gen 6:519-525 (References **AR, AU2, and AY2** in the Form PTO-1449 submitted on November 5, 2001). The techniques involved in the invention (*e.g.*, recombinant DNA technologies), all of which were well known in the art even before the filing date, are highly reliable and can be readily practiced by a skilled artisan. In accordance with the written description guidelines and the MPEP, "[i]nformation which is well known in the art need not be described in detail in the specification." Written Description Guidelines for the Examination of Patent Applications, section II, page 1105, column 3; MPEP 2163.

For the above reasons, Applicants maintain that all pending claims are supported by the specification with sufficient detail, and in light of the detailed description provided in the specification and the level of skill in the art, that Applicants were in possession of the claimed invention at the time this application was filed. Accordingly, reconsideration and withdrawal of rejection are respectfully requested.

Rejections of Claims 32-35, 37-46, and 48-51 under 35 U.S.C. § 112, Second Paragraph

The Examiner rejects claims 32-35, 37-46, and 48-51 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

a. The Examiner asserts that the phrase, in claim 32, "wherein said nucleotide sequence has been modified to contain one or more recognition sites for a restriction enzyme, such that digestion with a single restriction enzyme excises from said vector a restriction fragment" is vague and indefinite because it is unclear how multiple recognition sites can produce a single restriction fragment. See Office Action, page 9, lines 9-17.

Solely to expedite prosecution of the application, Applicants have amended independent claim 32 to recite "a recognition site," thereby rendering the rejection moot.

b. The Examiner asserts that the phrase, in claim 42, "[A] recombinant vector comprising an isolated nucleotide sequence encoding an snRNA, wherein said nucleotide sequence comprises an insertion cassette between two insertion sites," is vague and indefinite. Specifically, the Examiner asserts that "it is unclear how 'A' single recombinant vector can contain a 'cassette'? A cassette contains multiple sequences and, as a result, only a 'library' of sequences can contain such a limitation." See Office Action, the paragraph bridging pages 9 and 10.

Applicants respectfully disagree. Contrary to the Examiner's assertion, the specification clearly discloses that an insertion cassette is a single nucleotide sequence to be inserted into a single vector between two insertion sites. For example, the specification teaches that "[a]n insertion cassette of the invention can include **a** double-stranded DNA modification fragment containing any number of DNA base pairs. In embodiments, the

insertion cassette includes a double-stranded DNA sequence of about 5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55 or 60 base pairs." (page 4, lines 16-22, emphasis added; also see page 5, lines 1-18). Clarification of this rejection is respectfully requested.

In view of the above amendments and remarks, the Examiner is respectfully requested to reconsider and withdraw all rejections under 35 U.S.C. § 112, second paragraph.

Rejections of Claims 32-35, 37-46, and 48-51 under 35 U.S.C. § 112, First Paragraph

The Examiner rejects claims 33-35, 37-46, and 48-51 under 35 U.S.C. § 112, first paragraph, because of alleged non-enablement. Applicants respectfully traverse this rejection and contend that the rejection is moot in light of the amended claims.

As an initial matter, the Examiner asserts that "the specification, while being enabling for X, does not reasonably provide enablement for Y." See Office Action, page 10, lines 9-11 (emphasis added). Clarification is respectfully requested regarding the subject matter of X and Y.

It appears that the Examiner's rejection is mainly directed to the restriction enzyme as recited in the claims. Specifically, the Examiner asserts that "Applicants' claims encompass the use of Type I and Type III endonucleases that are inherently unpredictable to work with since there is no 'strict control' over the cut sites . . . In addition, a person of skill in the art would not expect a 'single cleavage' enzyme to excise a restriction fragment that includes that recognition site especially if that enzyme cleaves within its own recognition site." Office Action, page 11, lines 9-19.

Applicants have argued above that one of skill in the art would know that independent claims 32 and 42 relate to Type II, rather than Type I or III, restriction enzymes. Further, Applicants submit that the specification is broadly enabling for the amended claims, for example, with respect to utilization of the recognition sites for dual cleavage restriction enzymes for constructing vectors (see, *e.g.*, page 15, lines 13-29; page 16, lines 1-26; Example on pages 21-23). Applicants believe the Examiner's enablement rejections with respect to these claims have been obviated.

In addition, Applicants remind the Examiner that there is no legal requirement to test the efficacy of all species of the claimed invention to show the operativeness. The law does not impose such a formidable burden on inventors seeking patent protection. "Appellants (here, Applicants) are not required to disclose every species encompassed by their claims even in an unpredictable art" (emphasis original). *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976). Such a holding is only reasonable, since it is very difficult, if not impossible, to test and disclose all operative species in the chemical and biotechnology fields. As further pointed out by the Angstadt court "[w]ithout undue experimentation or effort or expense the combinations which do not work will readily be discovered and, of course, nobody will use them and the claims do not cover them." Id, at 219.

Applicants submit that the specification and the pending claims as amended enable one of skill in the art to practice the invention without undue experimentation. Applicants respectfully request that the Examiner withdraw the enablement rejection.

Rejections of Claims 32-34, 37-46, and 48-51 under 35 U.S.C. § 102(b)/ § 103(a)

Claims 32-34, 37-46, and 48-51 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Verhasselt *et al.* (Yeast, 1998, 13:241-250) as evidenced by Sears *et al.* and Genomenet EMBL-today Entry No. X89514. Applicants respectfully traverse this rejection and contend that the rejection is moot in light of the amended claims.

The standard for anticipating a claim is clearly outlined in MPEP 2131, and this standard is further supported by the Courts. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1978). Applicants contend that Verhasselt *et al.* fail to satisfy the criteria for anticipating the present invention.

Solely for greater clarity, Applicants have amended independent claim 32 to recite that said snRNA-encoding nucleotide sequence has been modified to contain a recognition site for a dual cleavage restriction enzyme. Similarly, independent claim 42 has been

amended to recite that said snRNA-encoding nucleotide sequence comprises an insertion cassette between two insertion sites, wherein said two insertion sites are formed by digestion with a single double cleavage restriction enzyme to excise from said vector a restriction fragment that contains a recognition site for said restriction enzyme. Applicants submit that the pending claims as amended are neither anticipated nor rendered obvious by Verhasselt *et al.*

Verhasselt *et al.* disclose a 37.6-kb cosmid sequence isolated from yeast which comprises a gene encoding an snRNA (snR6). This snR6-encoding gene (designated as Gene Element L2910) is located between positions 2843-2954 of Entry No. X89514 (see Verhasselt *et al.*, page 243, Table 1; and Genomenet EMBL-today Entry No. X89514, page 2). By contrast, a BaeI recognition site is located at positions 5864-5874 of X89514 (*i.e.*, Gene Element L2916), which is **outside** the snRNA-encoding gene (*i.e.*, Gene Element L2910). See Genomenet EMBL-today Entry No. X89514, page 9.

In addition, Verhasselt *et al.* do **not** teach that the snRNA-encoding gene (*i.e.*, Gene Element L2910) has been modified to contain a recognition site as recited in independent claim 32 or 42 (*e.g.*, BaeI). Moreover, Verhasselt *et al.* do **not** teach that the snRNA-encoding gene (*i.e.*, Gene Element L2910) has been modified to comprise an insertion cassette between two insertion sites as recited in independent claim 42. Thus, Verhasselt *et al.* fail to teach the invention as recited in claim 32 or 42. For the above reasons, Applicants submit that independent claim 32 and 42 as well as their dependent claims are not anticipated by Verhasselt *et al.*

Applicants further traverse the rejection under 35 U.S.C. § 103(a). Pursuant to MPEP 2143 and in view of *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), "[t]o establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations."

Applicants have presented the arguments above that Verhasselt *et al.* simply do not teach all the claim limitations, including, but not limited to, modifying an snRNA-encoding nucleotide to include a recognition site (*e.g.*, BaeI) or to comprise an insertion cassette between two insertion sites. The Examiner has not cited any other reference which bridges the gap between Verhasselt *et al.* and the claimed invention. Further, Applicants submit that Verhasselt *et al.* fail to provide any suggestion or motivation for one of skill in the art to develop a recombinant vector which comprises a modified snRNA-encoding nucleotide sequence as recited in the instant application. In the absence of any guidance that the 37.6-kb cosmid of Verhasselt *et al.* should be modified in some way, for example, within the snRNA-encoding gene, one of ordinary skill in the art would have had no motivation to perform the invention claimed in the present application.

In view of the above, Applicants submit that the instant claims are not rendered obvious by Verhasselt *et al.* Reconsideration and withdrawal of the obviousness rejection are respectfully requested.

Rejections of Claims 32-35, 38-46, and 48-51 under 35 U.S.C. § 102(b)/ § 103(a)

Claims 32-35, 38-46, and 48-51 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Shambaugh *et al.* (Molecular and Biochemical Parasitology 1994, 64, 349-352) as evidenced by Sears *et al.* and NCBI Entry No. L22246. Applicants respectfully traverse this rejection and contend that the rejection is moot in light of the amended claims.

Shambaugh *et al.* disclose an about 6-kb DNA sequence (designed in NCBI Entry No. L22246) isolated from *Ascaris lumbricoids* which contain four U1 snRNA genes. The four U1 snRNA-encoding genes are located at positions 2071-2236, 3195-3358, 4551-4715, and 5535-5700 of Entry No. L22246, respectively (see NCBI Entry No. L22246, page 1). By contrast, a BaeI recognition site is located at positions 348-358 of L22246, which is **outside** any of the four U1 snRNA-encoding genes.

In addition, Shambaugh *et al.* do **not** teach that any of the U1 snRNA-encoding genes has been modified to contain a recognition site as recited in independent claim 32 or 42 (*e.g.*, BaeI). Moreover, Shambaugh *et al.* do **not** teach that any of the U1 snRNA-encoding genes

has been modified to comprise an insertion cassette between two insertion sites as recited in independent claim 42. Thus, Shambaugh *et al.* fail to teach the invention as recited in claim 32 or 42. For the above reasons, Applicants submit that independent claim 32 and 42 as well as their dependent claims are not anticipated by Shambaugh *et al.*

Applicants further traverse the rejection under 35 U.S.C. § 103(a). Pursuant to MPEP 2143 and in view of *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), "[t]o establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations."

Applicants have presented the arguments above that Shambaugh *et al.* simply do not teach all the claim limitations, including, but not limited to, modifying an snRNA-encoding nucleotide to include a recognition site (*e.g.*, BaeI) or to comprise an insertion cassette between two insertion sites. The Examiner has not cited any other reference which bridges the gap between Shambaugh *et al.* and the claimed invention. Further, Applicants submit that Shambaugh *et al.* fail to provide any suggestion or motivation for one of skill in the art to develop a recombinant vector which comprises a modified snRNA-encoding nucleotide sequence as recited in the instant application. In the absence of any guidance that the about 6-kb DNA sequence of Shambaugh *et al.* should be modified in some way, for example, within one of the four U1 snRNA-encoding genes, one of ordinary skill in the art would have had no motivation to perform the invention claimed in the present application.

In view of the above, Applicants submit that the instant claims are not rendered obvious by Shambaugh *et al.* Reconsideration and withdrawal of the obviousness rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Please charge any deficiency or credit any overpayment in the fees that may be due in this matter to **Deposit Account No. 18-1945, under Order No. WIBL-P01-523.**

Dated: July 10, 2007

Respectfully submitted,

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